CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074969

Trade Name : ACYCLOVIR SODIUM FOR INJECTION

Generic Name: Acyclovir Sodium for Injection, 500mg (base)/vial and 1Gm (base)/vial

Sponsor : Gensia Laboratories, Ltd.

Approval Date: August 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074969

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074969

APPROVAL LETTER

ANDA 74-969

AUG 26 1997

Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92718-1902

Dear Sir:

This is in reference to your abbreviated new drug application dated September 30, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium for Injection, 500 mg (base)/vial and 1 g (base)/vial.

Reference is also made to your amendments dated May 23 and August 12, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Sodium for Injection, 500 mg (base)/vial and 1 g (base)/vial to be bioequivalent and, therefore therapeutically equivalent to that of the listed drug (Zovirax® Sterile Powder, 500 mg (base)/vial and 1 g (base)/vial of Glaxo Wellcome, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

8/26/97

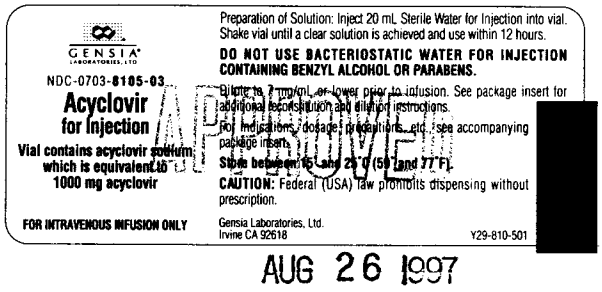
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074969

FINAL PRINTED LABELING

Vial Label/Shelf Pack A Label - NDC #0703-8105-03
(Part #Y29-810-501)

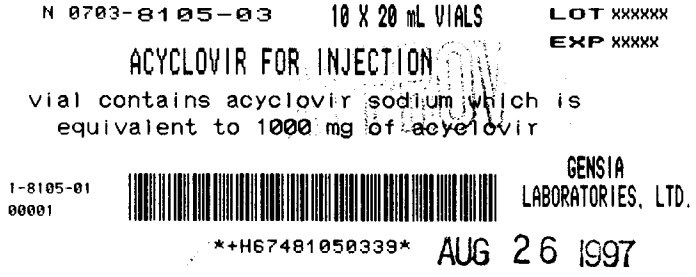
1000 mg/20 mL vial



AUG 26 1997

Shelf Pack B Label - NDC #0703-8105-03
(Part #1-8105-01)

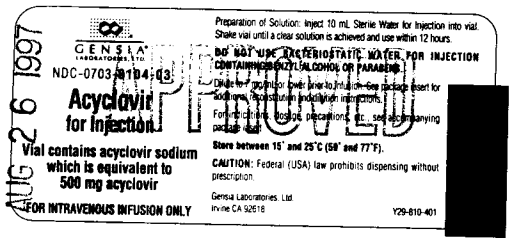
1000 mg/20 mL vial



AUG 26 1997

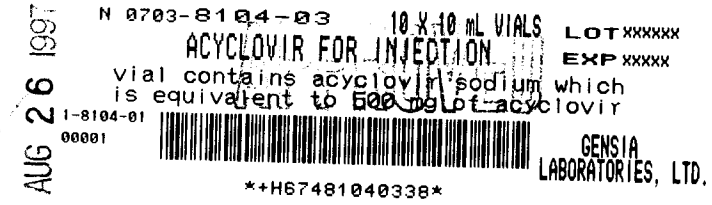
Vial Label/Shelf Pack A Label - NDC #0703-8104-03
(Part #Y29-810-401)

500 mg/10 mL vial



Shelf Pack B Label - NDC #0703-8104-03
(Part #1-8104-01)

500 mg/10 mL vial



Y36-202-501
Package Insert

GENSIA®
LABORATORIES, LTD.

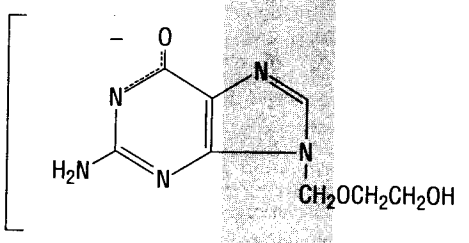
Acyclovir for Injection

FOR INTRAVENOUS INFUSION ONLY

DESCRIPTION

Acyclovir for Injection is an antiviral drug active against herpes viruses. **Acyclovir for Injection** is a formulation for intravenous administration. Each 5.49 mg of sterile lyophilized acyclovir sodium is equivalent to 5 mg acyclovir.

The chemical name of acyclovir sodium is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy) methyl]-6*H*-purin-6-one monosodium salt; it has the following structural formula:



Molecular Formula: $C_8H_{10}N_5NaO_3$

Acyclovir sodium is a white, crystalline powder with a molecular weight of 247 and a solubility in water exceeding 100 mg/mL. Each 500 mg or 1000 mg vial of **Acyclovir for Injection** when reconstituted with 10 mL or 20 mL, respectively, sterile diluent yields 50 mg/mL acyclovir (pH range between 11 and 12). Further dilution in any appropriate intravenous solution must be performed before infusion (see **DOSAGE AND ADMINISRATION, Method of Preparation**). At physiologic pH, acyclovir exists as the un-ionized form with a molecular weight of 225 and a maximum solubility of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV, and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with Herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology: The quantitative relationship between the *in vitro* susceptibility of herpes simplex virus to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤0.9 mcg/mL acyclovir, and 50% of all isolates were sensitive to ≤0.2 mcg/mL of acyclovir. For HSV-2 isolates, 90% were sensitive to ≤2.2 mcg/mL; and 50% of all isolates were sensitive to ≤0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics: The pharmacokinetics of acyclovir has been evaluated in 95 patients (9 studies). Results were obtained in adult patients with normal renal function during Phase 1/2 studies after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 15 mg/kg every 8 hours. Pharmacokinetics was also determined in pediatric patients with normal renal function ranging in age from 1 to 17 years at doses of 250 mg/m^2 or 500 mg/m^2 every 8 hours. In these studies, dose-independent pharmacokinetics is observed in the range of 0.5 to 15 mg/kg. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing.[23] When acyclovir was administered to adults at 5 mg/kg (approximately 250 mg/m^2) by one-hour infusions every 8 hours, mean steady-state peak and trough concentrations of 9.8 mcg/mL (5.5 to 13.8 mcg/mL) and 0.7 mcg/mL (0.2 to 1.0 mcg/mL), respectively, were achieved. Similar concentrations are achieved in children over 1 year of age when doses of 250 mg/m^2 are given by one-hour infusions every 8 hours. At a dose of 10 mg/kg given by one-hour infusion every 8 hours, mean steady-state peak and trough concentrations were 22.9 mcg/mL (14.1 to 44.1 mcg/mL) and 1.9 mcg/mL (0.5 to 2.9 mcg/mL). Similar concentrations were achieved in children dosed at 500 mg/m^2 given by one-hour infusion every 8 hours. Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9% to 33%), and drug interactions involving binding site displacement are not anticipated.[23]

Renal excretion of unchanged drug by glomerular filtration and tubular secretion is the major route of acyclovir elimination accounting for 62% to 91% of the dose as determined by ^{14}C-labelled drug. The only major urinary metabolite detected is 9-carboxymethoxymethylguanine. This may account for up to 14.1% of the dose in patients with normal renal function. An insignificant amount of drug is recovered in feces and expired CO_2, and there is no evidence to suggest tissue retention;[23] however, postmortem examinations have shown that acyclovir is widely distributed in tissues and body fluids including brain, kidney, lung, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, cerebrospinal fluid, and herpetic vesicular fluid.

The half-life and total body clearance of acyclovir is dependent on renal function as shown below.[23]

Creatinine Clearance (mL/min/1.73m^2)	Half-Life (hr)	Total Body Clearance (mL/min/1.73m^2)
> 80	2.5	327
50-80	3.0	248
15-50	3.5	190
0 (Anuric)	19.5	29

Acyclovir was administered at a dose of 2.5 mg/kg to 6 adult patients with severe renal failure. The peak and trough plasma levels during the 47 hours preceding hemodialysis were 8.5 mcg/mL and 0.7 mcg/mL, respectively.[24,25]

Consult **DOSAGE AND ADMINISTRATION** section for recommended adjustments in dosing based upon creatinine clearance.

The half-life and total body clearance of acyclovir in pediatric patients over 1 year of age is similar to those in adults with normal renal function (see **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE

Acyclovir for Injection is indicated for the treatment of initial and recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) and varicella-zoster (shingles) infections in immunocompromised patients. It is also indicated for herpes simplex encephalitis in patients over 6 months of age and for severe initial clinical episodes of herpes genitalis in patients who are not immunocompromised.

Herpes Simplex Infections in Immunocompromised Patients

A multicenter trial of intravenous acyclovir at a dose of 250 mg/m^2 every 8 hours (750 mg/m^2/day) for 7 days was conducted in 98 immunocompromised patients (73 adults and 25 children) with oro-facial, esophageal, genital and other localized infections (52 treated with acyclovir and 46 with placebo). Acyclovir significantly decreased virus excretion, reduced pain, and promoted scabbing and rapid healing of lesions.[14,26,27,28]

Initial Episodes of Herpes Genitalis

In placebo-controlled trials, 58 patients with initial genital herpes were treated with intravenous acyclovir 5 mg/kg or placebo (27 patients treated with acyclovir and 31 treated with placebo) every 8 hours for 5 days. Acyclovir decreased the duration of viral excretion, new lesion formation, and duration of vesicles, and promoted healing of lesions.[28,29,30]

Herpes Simplex Encephalitis

Sixty-two patients ages 6 months to 79 years with brain biopsy-proven herpes simplex encephalitis were randomized to receive either acyclovir (30 mg/kg day) or adenine arabinoside (15 mg/kg/day) for 10 days (28 were treated with acyclovir and 34 with adenine

arabinoside).[31] Overall mortality at 6 months for patients treated with acyclovir was 18% compared to 59% for patients treated with adenine arabinoside ($P = 0.003$). The proportion of patients treated with acyclovir functioning normally or with only mild sequelae (e.g., decreased attention span) was 39% compared to 9% of patients treated with adenine arabinoside ($P = 0.01$). The remaining patients in both groups had moderate (e.g., hemiparesis, speech impediment, or seizure) or severe (continuous supportive care required) neurologic sequelae.

After 12 months of follow-up, two additional patients treated with acyclovir had died, resulting in an overall mortality of 25% compared to 59% for patients treated with adenine arabinoside ($P = 0.02$). Morbidity assessments at that time indicated that 32% of patients treated with acyclovir were functioning normally, or with only mild sequelae compared to 12% of patients treated with adenine arabinoside ($P = 0.06$). Moderate to severe impairment was noted in all remaining patients in both groups who were available for evaluation. Patients less than 30 years of age and those who had the least severe neurologic involvement at time of entry into study had the best outcome with treatment with acyclovir. An additional controlled study performed in Europe[32] demonstrated similar findings. The superiority of acyclovir over adenine arabinoside for neonatal herpes encephalitis has not been demonstrated.

Varicella-Zoster Infections in Immunocompromised Patients

A multicenter trial of **Acyclovir for Injection** at a dose of 500 mg/m^2 every 8 hours for 7 days was conducted in immunocompromised patients with zoster infections (shingles). Ninety-four (94) patients were evaluated (52 patients were treated with acyclovir and 42 with placebo). Acyclovir halted progression of infection as determined by significant reductions in cutaneous dissemination, visceral dissemination, or the proportion of patients deemed treatment failures.[28,33]

A comparative trial of acyclovir and vidarabine was conducted in 22 severely immunocompromised patients with zoster infections. Acyclovir was shown to be superior to vidarabine as demonstrated by significant differences in the time of new lesion formation, the time to pain reduction, the time to lesion crusting, the time to complete healing, the incidence of fever, and the duration of positive viral cultures. In addition, cutaneous dissemination occurred in none of the 10 patients treated with acyclovir compared to 5 of the 10 vidarabine recipients who presented with localized dermatomal disease.[34]

Diagnosis

Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. In initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. Whereas cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may assist in the diagnosis.[35]

The Tzanck smear does not distinguish varicella-zoster from herpes simplex infections. Culture of varicella-zoster is not widely available.

Herpes encephalitis should be confirmed by brain biopsy to obtain tissue for histologic examination and viral culture and to exclude other causes of neurologic disease. A presumptive diagnosis of herpes encephalitis may be made on the basis of focal changes in the temporal lobe visualized with various diagnostic methods including magnetic resonance imaging, computerized tomography, radionuclide scans, or electroencephalography. Culture of the cerebrospinal fluid for herpes simplex virus is unreliable.

CONTRAINDICATIONS

Acyclovir for Injection is contraindicated for patients who develop hypersensitivity to the drug.

WARNINGS

Acyclovir for Injection is intended for intravenous infusion only and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye. Intravenous infusions must be given over a period of at least 1 (one) hour to reduce the risk of renal tubular damage (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

General: The recommended dosage, frequency, and length of treatment should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Although the aqueous solubility of acyclovir sodium (for infusion) is >100 mg/mL, precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 mg/mL at 37°C in water) is exceeded or if the drug is administered by bolus injection. This complication causes a rise in serum creatinine and blood urea nitrogen (BUN), and a decrease in renal creatinine clearance. Ensuing renal tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Bolus administration of the drug leads to a 10% incidence of renal dysfunction, while in controlled studies, infusion of 5 mg/kg (250 mg/m^2) and 10 mg/kg (500 mg/m^2) over an hour was associated with a lower frequency—3.8%. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make further renal impairment with acyclovir more likely. In most instances, alterations of renal function were transient and resolved spontaneously or with improvement of water and electrolyte balance, drug dosage adjustment, or discontinuation of drug administration. However, in some instances, these changes may progress to acute renal failure.

Administration of acyclovir by intravenous infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first 2 hours following infusion, particular attention should be given to establishing sufficient urine flow during that period in order to prevent precipitation in renal tubules. Recommended urine output is ≥500 mL per gram of drug infused. In patients with encephalitis, the recommended hydration should be balanced by the risk of cerebral edema.

When dosage adjustments are required, they should be based on estimated creatinine clearance (see **DOSAGE AND ADMINISTRATION**).

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, or coma. Acyclovir should be used with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities or significant hypoxia. It should also be used with caution in patients who have manifested prior neurologic reactions to cytotoxic drugs or those receiving concomitant intrathecal methotrexate or interferon.

Exposure of HSV isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. These viruses usually are deficient in thymidine kinase (required for acyclovir activation) and are less pathogenic in animals. Similar isolates have been observed in severely immunocompromised patients during the course of controlled and uncontrolled studies of intravenously administered acyclovir. These occurred in patients with severe combined immunodeficiencies or following bone marrow transplantation. The presence of these viruses was not associated with a worsening of clinical illness; and in some instances, the virus disappeared spontaneously. The possibility of the appearance of less sensitive viruses must be recognized when treating such patients.[11-19] The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has not been established.

Drug Interactions: Co-administration of probenecid with acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[36] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 30 mg/kg/day (10 mg/kg/every 8 hours, dosing appropriate for treatment of herpes zoster or herpes encephalitis), or 15 mg/kg/day (5 mg/kg/every 8 hours, dosing appropriate for treatment of primary genital herpes or herpes simplex infections in immunocompromised patients). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations in both the mouse and rat bioassays were lower than concentrations in humans.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (3 to 5 times human levels) in one system; and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (3 to 6 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (5 to 10 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (31 to 61 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (3 to 6 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 13 to 25 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 20 to 40 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 150 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 120 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were the same as human levels. At 50 mg/kg/day, s.c. in the rat (1 to 2 times human levels), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (1 to 3 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (4 to 9 times human levels). In a rat peri- and post-natal study at 50 mg/kg/day, s.c. (1 to 2 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (4 to 9 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 months and 1 month, respectively, caused testicular atrophy. Plasma levels were not measured in the one-month study and were 2 to 4 times human levels in the six-month study. Testicular atrophy was persistent through the four-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day, plasma levels were 4 to 8 times human levels, while at 200 mg/kg/day, they were 13 to 25 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for 1 month (2 to 3 times human plasma levels) and in dogs given 60 mg/kg/day orally for 1 year (the same as human plasma levels).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures in the above studies resulted in plasma levels 4 and 9, and 1 and 2 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[37] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation

day 10, resulting in plasma levels 5 to 10 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[38-39] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

ADVERSE REACTIONS

The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received acyclovir at ~ 5 mg/kg (250 mg/m²) three times daily, and approximately 300 patients who received ~ 10 mg/kg (500 mg/m²) three times daily.

The most frequent adverse reactions reported during administration of intravenous acyclovir were inflammation or phlebitis at the injection site in approximately 9% of the patients and transient elevations of serum creatinine or BUN in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] intravenous infusion). Nausea and/or vomiting occurred in approximately 7% of the patients (the majority occurring in nonhospitalized patients who received 10 mg/kg). Itching, rash, or hives occurred in approximately 2% of patients. Elevation of transaminases occurred in 1% to 2% of patients.

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, or coma (see **PRECAUTIONS**).

Adverse reactions which occurred at a frequency of less than 1% and which were probably or possibly related to intravenous administration of acyclovir were: anemia, anuria, hematuria, hypotension, edema, anorexia, lightheadedness, thirst, headache, diaphoresis, fever, neutropenia, thrombocytopenia, abnormal urinalysis (characterized by an increase in formed elements in urine sediment), and pain on urination.

Other reactions have been reported with a frequency of less than 1% in patients receiving acyclovir, but a causal relationship between acyclovir and the reaction could not be determined. These include pulmonary edema with cardiac tamponade, abdominal pain, chest pain, thrombocytosis, leukocytosis, neutrophilia, ischemia of digits, hypokalemia, purpura fulminans, pressure on urination, hemoglobinemia, and rigors.

Observed During Clinical Practice: Based on clinical practice experience in patients treated with intravenous acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, pain, and rarely, anaphylaxis

Digestive: elevated liver function tests, nausea

Hemic and Lymphatic: leukopenia

Nervous: agitation, coma, confusion, convulsions, delirium, hallucinations, obtundation, psychosis

Skin: rash

Urogenital: elevated blood urea nitrogen, elevated creatinine, renal failure

OVERDOSAGE

Overdosage has been reported following administration of bolus injections, or inappropriately high doses, and in patients whose fluid and electrolyte balance was not properly monitored. This has resulted in elevations in BUN, serum creatinine, and subsequent renal failure. Lethargy, convulsions, and coma have been reported rarely.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded (see **PRECAUTIONS**). Renal lesions related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. In the event of overdosage, sufficient urine flow must be maintained to prevent precipitation of drug in renal tubules. Recommended urine output is ≥500 mL per gram of drug infused. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION: CAUTION—RAPID OR BOLUS INTRAVENOUS AND INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED. Therapy should be initiated as early as possible following onset of signs and symptoms. For diagnosis—see INDICATIONS.

Dosage:

HERPES SIMPLEX INFECTIONS

MUCOSAL AND CUTANEOUS HERPES SIMPLEX (HSV-1 and HSV-2) INFECTIONS IN IMMUNOCOMPROMISED PATIENTS—5 mg/kg infused at a constant rate over 1 hour, every 8 hours (15 mg/kg/day) for 7 days in adult patients with normal renal function. In children under 12 years of age, more accurate dosing can be attained by infusing 250 mg/m² at a constant rate over 1 hour, every 8 hours (750 mg/m²/day) for 7 days.

SEVERE INITIAL CLINICAL EPISODES OF HERPES GENITALIS—The same dose given above—administered for 5 days.

HERPES SIMPLEX ENCEPHALITIS—10 mg/kg infused at a constant rate over at least 1 hour, every 8 hours for 10 days. In children between 6 months and 12 years of age, more accurate dosing is achieved by infusing 500 mg/m², at a constant rate over at least one hour, every 8 hours for 10 days.

VARICELLA ZOSTER INFECTIONS

ZOSTER IN IMMUNOCOMPROMISED PATIENTS—10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days in adult patients with normal renal function. In children under 12 years of age, equivalent plasma concentrations are attained by infusing 500 mg/m² at a constant rate over at least 1 hour, every 8 hours for 7 days. Obese patients should be dosed at 10 mg/kg (Ideal Body Weight). A maximum dose equivalent to 500 mg/m² every 8 hours should not be exceeded for any patient.

PATIENTS WITH ACUTE OR CHRONIC RENAL IMPAIRMENT: Refer to **DOSAGE AND ADMINISTRATION** section for recommended doses, and adjust the dosing interval as indicated in the table below:

Creatinine Clearance (mL/min/1.73m²)	Percent of Recommended Dose	Dosing Interval (hours)
>50	100%	8
25-50	100%	12
10-25	100%	24
0-10	50%	24

Hemodialysis: For patients who require dialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[24,25]

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.[40,41]

Method of Preparation: Each 10 mL vial contains acyclovir sodium equivalent to 500 mg of acyclovir. Each 20 mL vial contains acyclovir sodium equivalent to 1000 mg of acyclovir. The contents of the vial should be dissolved in Sterile Water for Injection as follows:

Contents of Vial	Amount of Diluent
500 mg	10 mL
1000 mg	20 mL

The resulting solution in each case contains 50 mg acyclovir per mL (pH range between 11 and 12). Shake the vial well to assure complete dissolution before measuring and transferring each individual dose. **DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS.**

Administration: The calculated dose should then be removed and added to any appropriate intravenous solution at a volume selected for administration during each one-hour infusion. Infusion concentrations of approximately 7 mg/mL or lower are recommended. In clinical studies, the average 70 kg adult received between 60 and 150 mL of fluid per dose. Higher concentrations (e.g., 10 mg/mL) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Standard, commercially available electrolyte and glucose solutions are suitable for intravenous administration; biologic or colloidal fluids (e.g., blood products, protein solutions, etc.) are not recommended.

Once in a solution in the vial at a concentration of 50 mg/mL, the drug should be used within 12 hours. Once diluted for administration, each dose should be used within 24 hours. Refrigeration of reconstituted solutions may result in formation of a precipitate which will redissolve at room temperature.

Parenteral drug products should be inspected visually for particulate mater and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: Acyclovir for Injection, lyophilized, is supplied as follows:

NDC Number	Acyclovir for Injection	Vial Size	Packaged
N0703-**8104-03**	500 mg	10 mL vial	10 per shelf tray
N0703-**8105-03**	1000 mg	20 mL vial	10 per shelf tray

Store between 15° and 25°C (59° and 77°F).

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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Issued: May 1997

Gensia Laboratories, Ltd.
Irvine CA 92618

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074969

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-969

3. NAME AND ADDRESS OF APPLICANT
Gensia Laboratories, Ltd.
Attention: Donald J. Harrigan, R.Ph.
19 Hughes
Irvine, CA 92718-1902

4. LEGAL BASIS FOR SUBMISSION
The Reference Listed Drug is Zovirax® Sterile Powder (Acyclovir Sodium) manufactured by Glaxo Wellcome Co. pursuant to NDA 18-603. Gensia certified that to the best of its knowledge patent # 4199574 held by Glaxo Wellcome expired on April 22, 1997. Additionally, Glaxo Wellcome has not been granted a period of marketing exclusivity for Zovirax® Sterile Powder.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME
Acyclovir Sodium

8. SUPPLEMENTS PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: September 30, 1996
Amendment: May 23, 1997 (Subject of this review)
Amendment: August 12, 1997 (Subject of this review)

FDA:
Acknowledgment: December 27, 1996
Micro Review: January 15, 1997
Bio letter: February 4, 1997
Label Review: March 21, 1997
Letter; C.R. # 1: May 7, 1997

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

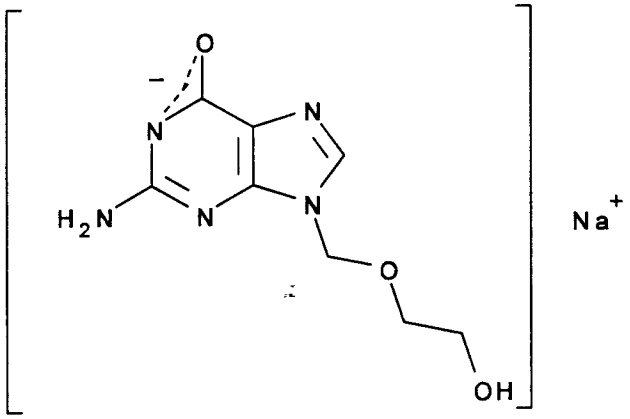
13. DOSAGE FORM
Powder for Injection
(Lyophilized)

14. POTENCY
50 mg/mL (10 mL & 20 mL vials)

15. CHEMICAL NAME AND STRUCTURE:

Acyclovir Sodium

$C_8H_{10}N_5NaO_3$; M.W. = 247.19



9-[(2-Hydroxyethoxy)methyl]guanine monosodium salt.
CAS [69657-51-8]

16. RECORDS AND REPORTS: N/A

17. COMMENTS
a. CMC issues satisfactorily resolved in the 5/23/97 amendment.
b. Bio satisfactory 1/16/97 & 3/13/97.
c. Label review satisfactory 6/26/97.
d. EIR acceptable 6/24/97.
e. Microbiological review satisfactory 6/10/97.
f. Methods validation satisfactory with comment 8/6/97.
g. DMF [redacted] satisfactory 6/9/97.

18. CONCLUSIONS AND RECOMMENDATIONS
This application can be approved.

19. REVIEWER:
Donald Shostak

DATE COMPLETED:
June 9, 1997
(Revised - micro, labeling 7/9/97)
(Revised - Methods validation 8/13/97)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074969

BIOEQUIVALENCE REVIEW(S)

ANDA 74-969

Gensia Laboratories, LTD.
Attention: Donald Harrigan, R.Ph.
19 Hughes
Irvine CA 92618

FEB - 4 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Sodium for Injection, 50 mg/mL.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 16 1997

Acyclovir Sodium for Injection
50 mg/ml
ANDA # 74-969
Reviewer: Hoainhon Nguyen
WP # 74969w.996

Gensia Laboratories
Irvine, California
Submission Date:
September 30, 1996

Review of a Waiver Request

The firm has requested a waiver from in vivo bioavailability requirements for its Acyclovir Sodium for Injection, 50 mg/ml, in 500 mg and 1000 mg vials, in accordance with 21 CFR 320.22 (b) (1).

Comments:

1. The test product, when reconsituted, is a solution intended for intravenous administration.

2. The formulation of the test product is identical to that of the currently approved Zovirax[R] Sterile Powder (acyclovir sodium), 50 mg/ml (when reconstituted), in 500 mg and 1000 mg vials, manufactured by Glaxo Wellcome, as shown below:

Ingredients	Zovirax[R] Formula	Gensia's Formula
Acyclovir Sodium	54.9 mg*	54.9 mg*
Hydrochloric Acid, NF	pH adjustment	pH adjustment
Sodium Hydroxide, NF	pH adjustment	pH adjustment
Water for Injection, USP**	q.s.	q.s.

*Equivalent to 50.0 mg Acyclovir
**Used during formulation: Product is lyophilized

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Gensia Laboratories demonstrates that its Acyclovir Sodium for Injection, 50 mg/ml, in 500 mg and 1000 mg vials, falls under 21 CFR 320.22 (b) (1) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of in vivo bioavailability study be granted. The test product is deemed bioequivalent to the currently approved Zovirax® Sterile Powder (acyclovir sodium), 50 mg/ml when reconstituted, in 500 mg and 1000 mg vials, manufactured by Glaxo Wellcome.

/S/ 1-16-97

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 1/16/97

HNguyen/01-15-97/WP # 74969w.996

cc: ANDA # 74-969 (original, duplicate), HFD-652 (Huang, Nguyen), Drug File, Division File